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Systematic Chromosome Examination of Two Families With Schizophrenia and Two Families With Manic Depressive Illness

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Systematic and detailed chromosome analysis, combined with a semistructured interview, was performed in 2 families with schizophrenia and in 2 families with manic depressive illness. Prometaphase technique did not reveal any subtle structural chromosome abnormalities. However, in standard techniques, gain and loss of sex chromosomes were observed. This occurred in patients at a younger age than in unaffected persons. This gives rise to the suspicion that sex chromosome aneuploidy may somehow be related to the development of psychosis. But since the data set is small, especially with respect to schizophrenia, further studies are needed to elucidate this observation. In one family, cosegregation of the disease locus with a marker on chromosome 21 was seen. Therefore, further research should determine if chromosome 21 contains a gene for manic depressive illness.

KEY WORDS: sex chromosome aneuploidy, marker chromosome no 21, psychosis

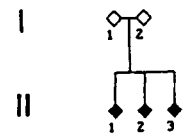
INTRODUCTION

Inheritance plays a role in the development of psychosis. Positional cloning, as well as a candidate gene approach, has been used in the hope of finding one or more relevant major genes. Cytogenetic studies may be helpful in the candidate gene approach. Many different loci have been proposed on cytogenetic evidence, but could not be confirmed by independent investigators. [reviewed by Basset, 1992; DeLisi et al., 1994]. To find such loci, we have made a systematic search for chromosome aberrations and normal chromosome variations in 2 families with manic depressive illness and 2 families with schizophrenia.

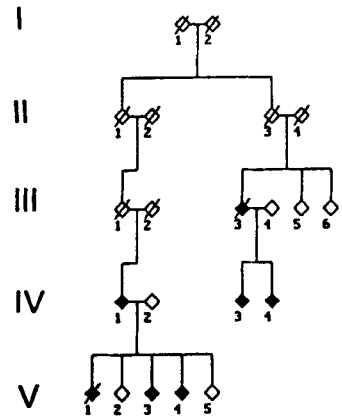
MATERIALS AND METHODS

The material comprises 2 families (16 persons) where schizophrenia was observed in several members (Fig. 1), and 2 families (56 persons) with manic depressive illness (Fig. 2).

In all participating family members a semistructured interview was performed (by H.E. and O.M) using



Family 1



Family 3

Fig. 1. Pedigree of families 1 and 3. ◆ suffer from schizophrenia.

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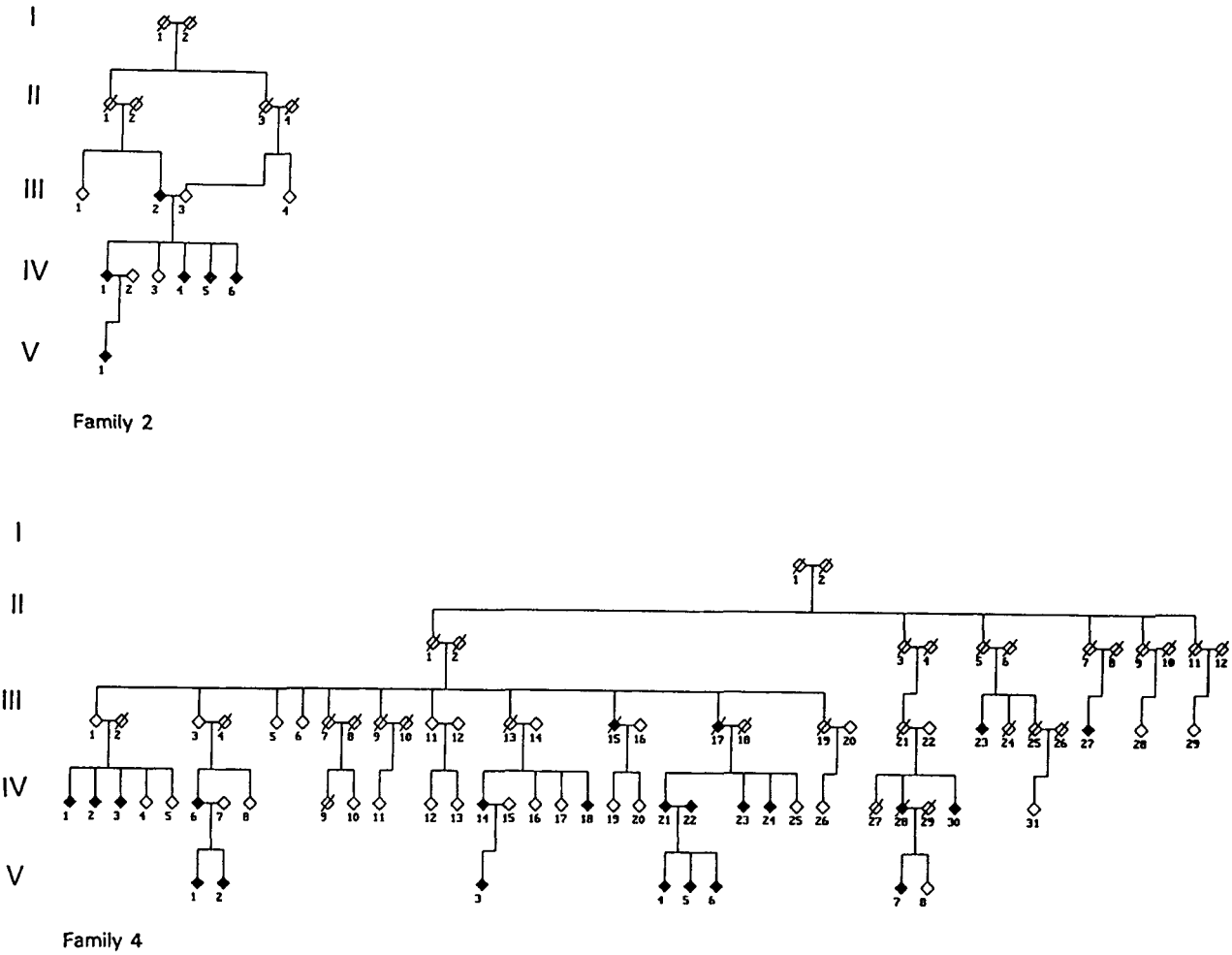

Fig. 2. Pedigree of families 2 and 4. ◆ suffer from manic depressive psychosis.

"Present State Examination," 10th edition [Wing et al., 1990]. Furthermore, diagnostic information was obtained from relatives, and medical records from admissions and general practitioners. A narrative was written on the basis of the above-mentioned sources. The narrative and the medical records were reviewed by a senior psychiatrist without knowledge of the family relations and diagnosis of the probands. He made the final diagnosis according to the *International Classification of Diseases, Diagnostic Criteria for Research*, 10th edition World Health Organization, 1993].

A broad phenotypic model was used. In the 2 schizophrenic families (Fig. 1), individuals suffering from schizophrenia (n = 7), delusional disorder (n = 1), and paranoid personality disorder (n = 1) were counted as affected. The only other psychiatric illness found was psychotic depression (family 3; III-3). In the 2 families with manic depressive illness, bipolar disorder, major single or recurrent depression, and recurrent minor depression were scored as affected. No patients with schizophrenia were found. Only 2 persons with anxiety disorders were scored as unaffected.

Chromosome studies were performed on cultures from peripheral blood. Prometaphase examination was performed in participants on preparations stained with acridine orange. Five–10 prometaphases were photographed and analyzed by projection. This technique was employed to increase the chance of detecting subtle chromosome aberrations.

Furthermore, in all persons standard 72-hr lymphocyte cultures were also performed. The preparations were stained with quinacrine mustard. From each person, 10–15 metaphases were photographed and analyzed by projection. The normal chromosome variants in the centromere regions of pairs 1, 3, 4, 9, and 16, as well as the satellites of the acrocentric chromosomes, were evaluated as linkage markers. Since during analysis we observed an astonishingly high rate of sex chromosome aneuploidy, we decided to perform a statistical analysis, systematically using the first 10 cells photographed by each person for evaluation of gain and loss of sex chromosomes.

The study was performed blindly. The cytogeneticist (U.F.) was not informed about subjects' psychiatric status.

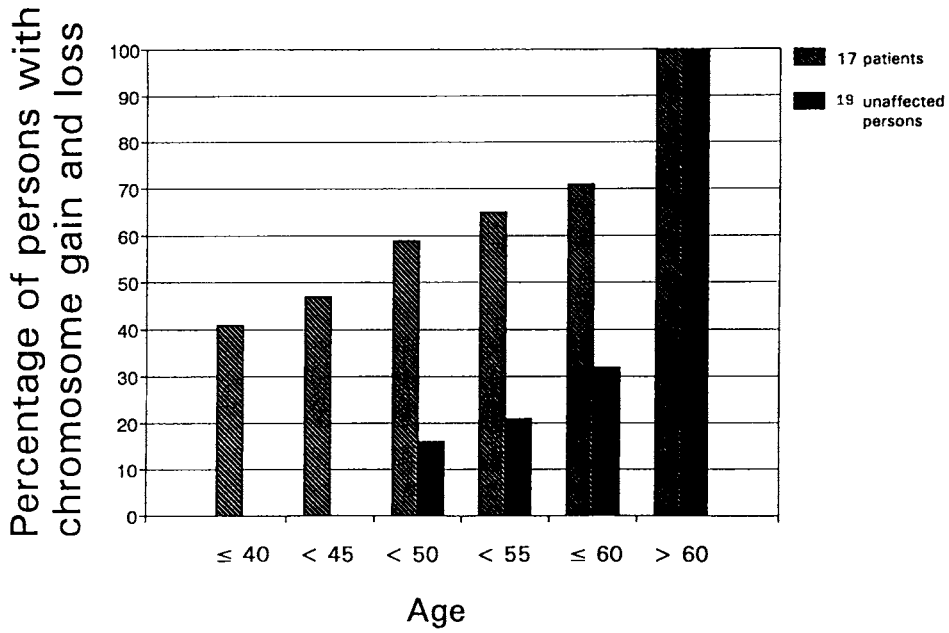

Fig. 3. Accumulative relative frequencies of patients with chromosome gain and loss compared to unaffected family members, stratified according to age.

RESULTS

Numerical Chromosome Abnormalities

The most consistent finding was the presence of hypo- or hyperdiploidy of sex chromosomes in single cells. Sex chromosome aneuploidy was observed in 17 of the 33 patients, and in 19 of the 45 unaffected members of the families. The difference is statistically not significant (Fisher's test, $P = 0.43$). Nor is there any significant difference between patients with schizophrenia and with manic depressive illness.

Since sex chromosome aneuploidy is normally associated with increasing age, the family members have been stratified according to age. No significant difference was found in gain and loss of sex chromosomes when comparing persons above age 50 years with persons below age 50 years (Mantel-Haenzsel test, $P = 0.12$) (Table I). When the material is stratified in 5 year-age intervals, it is seen that sex chromosome loss and gain starts earlier in patients than in unaffected family members (Fig. 3 and Table II). Group frequencies are significantly different between patients and controls (two-sided rank correlation test, $P = 0.0052$).

Structural Chromosome Abnormalities

None of the 16 individuals from the 2 families with schizophrenia had structural abnormalities. Translocations, deletions, and inversions in single cells were observed in patients as well as in unaffected individuals in the 2 families with manic depressive illness. There were as many patients as unaffected individuals with structural chromosome abnormalities. In one 49-year-old patient (family 4, IV-21), two of 26 cells showed a double translocation: t(1;6)(q32;q26) and t(9;11)(q34;q23), respectively. One unaffected individual, married into the family (family 4, III-16), had an inversion in one chromosome 1: (inv(1)(q12q42)) in 3 of 15 cells.

TABLE I. Number of Persons With Gain and Loss of Sex Chromosomes Stratified in Age Groups Below and Above 50 Years

	X aneuploidy in patients				X aneuploidy in unaffected individuals				
	Present		Absent		Present		Absent		
Family	≤50	>50	≤50	>50	≤50	>50	≤50	>50	Total
1[a]	1		2			2			5
2[b]	3	1	2			2	2		10
3[a]		1	2	2		2	2	3	12
4[b]	6	5	5	3	3	10	4	15	51
	10	7	11	5	3	16	8	18	78

[a]Schizophrenia.
[b]Manic depressive illness.

TABLE II. Number of Persons With Gain and Loss of Sex Chromosomes Stratified in Age Groups of 5-year Intervals

	≤40	41–45	46–50	51–55	56–60	≥61	Total
Patients	7	1	2	1	1	5	17
Controls	0	0	3	1	2	13	19
Total	7	1	5	2	3	18	36

In the 5 affected patients with structural abnormalities in single cells, the breakpoints were localized in 1q11, 1q32, 3p24, 5p15, 5q23, 6q26, 9q34, 10p11, 11p13, 11q23, 12q15, 13q31, 16q11, and 18q23. In the 10 unaffected persons, the breakpoints were in 1p32, 1p12, 1q42, 2p11, 6q21, 7p22, 12q21, 13q34, 17p11, and 20p11. None of the breakpoints occurred more than once.

Cosegregation of Marker Chromosomes With Disease

In family 1, all 3 sibs had the same heteromorphic chromosomes 13 and 15 from parent I-1, and the same chromosome 21 from parent I-2. No specific markers were segregating in family 3 with schizophrenia. In family 2 with manic depressive illness, all 5 affected children had inherited a chromosome 21 with the same heteromorphism of the satellite region from their respective affected parents. The probability of this is 0.031. None of the unaffected had this chromosome. In family 4, no specific markers were observed in the affected, which were not at the same time present in the unaffected.

DISCUSSION

So far, no systematic cytogenetic examinations have been performed on psychiatric patients and their healthy family members using standardized diagnostic concepts. Prometaphase technique and standard techniques specifically stained with quinacrine mustard for the detection of chromosome heteromorphism have been employed. In the present study, we have focused on these techniques with the hope of disclosing chromosome regions in which to search for genes for psychiatric illnesses.

We observed sex chromosome gain or loss in patients as well as in healthy family members. Age-related gains and losses of sex chromosomes are well-known [Fitzgerald and McEwan, 1977; Ford and Russel, 1985]. Kaplan [1970] speculated about possible correlation between sex chromosome mosaicism and schizophrenia, and DeLisi et al. [1994] concluded in a review article that X chromosome instability in general predisposes to psychosis, and that a specific locus for psychosis is located on the sex chromosomes. But the significance of this finding is difficult to interpret, because age of patients with sex chromosome aneuploidy is often not recorded, and the psychiatric diagnosis does not satisfy present diagnostic criteria. Only two cytogenetic studies on DMSIII-diagnosed patients have been published so far [DeLisi et al., 1994]. Among 64 males with schizophrenia, one had Klinefelter's syndrome with karyotype 47,XXY. Among 49 females with schizophrenia, one had a Turner mosaic and four had other X chromosome mosaics. The ages of these females were 47, 55, 56, and 57 years. The question arises whether these mosaics are due to high age or are correlated to the mental illness. Our study indicates that patients demonstrate sex chromosome gain and loss at a younger age than unaffected persons. Whether they have been true mosaics from birth or whether sex chromosome aneuploidy has arisen during their later life cannot be disclosed by this type of study. The results of our study give rise to the suspicion that sex chromosome aneuploidy may somehow be related to the development of psychosis. Our results, based on a very small group of patients, are in favour of the DeLisi et al.'s hypothesis (1994). But more systematic cytogenetic studies on larger materials are needed to elucidate this problem.

Structural chromosome aberrations in single cells were observed in patients as well as unaffected family members in the two families with manic depressive illness. There were two patients who had several single cells with different translocations and deletions. One patient was treated with Saroten, Cisordinol, and Lysantin, and the structural abnormalities could therefore be explained as toxic influence on the chromosomes. The other patient had no psychopharmacological treatment, but suffered from sclerordermia, which at that time had not been medicamentally treated. None of the breakpoints were observed more than once, either in the patients or in their family members. Only one of the breakpoints, which we analyzed in single cells, has earlier been observed in the literature in a patient with major affective disorder, namely 11q23.3-25 (Craddock et al., 1993). Most of the described structural abnormalities in these families may not have any relation to a disease gene that could be used in an attempt to localize the gene.

Co-segregation of a chromosomal marker with the disease locus was observed only in family 2, where all affected with manic depressive illness had a chromosome no. 21 with the same heteromorphism in the satellite region. If, in this family, we suspect a disease allele to be close to the centromere region of no. 21, it would be worth while to search in this region with different DNA markers. Previously, a variant chromosome no. 21 was described in an Arab mother and her daughter who both suffered from manic depressive illness. But, unfortunately, none of the other family members could be cytogenetically examined to elucidate the significance of this finding (El-Badramany et al., 1989). Chromosome no. 21 is also interesting because Straub et al. (1994) have recently found evidence of linkage to markers on 21q22.3 in manic depressive illness.

CONCLUSION

Although we used systematic and detailed chromosome analysis combined with semistructured interviews no definite results in regard to specific chromosome aberrations in psychiatric illness have been found. The data set is small, especially with respect to schizophrenia. Further studies are needed.

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